Case

- 45 yo male returned home to Tennessee from 9 day trip to Brazil (Amazon River trip) presenting with fever (102.2°F), headache, myalgias, arthralgias, and chills
- CBC: WBC 3.2, H/H 14.2/40, Plt 131
- Chem: BUN/Cr 13/1.5, AST 214, AlkPhos 35, Tbili 0.52
- ER treats with IV fluids and “pain meds” with presumed Dengue (discharged with outpatient follow-up)

Case

- Patient returns 3 days later with recurrent headache, and new nausea/vomiting, abdominal pain, and dizziness

- Appeared ill on exam
- VS: 101.5° F, HR 92, BP 102/74 (with orthostatic changes)
- EXAM FINDINGS: icteric sclera (“yellow eyes”), hepatomegaly, epigastric tenderness

- CBC: WBC 1.4, H/H 16.7/47, Plt 72
- Chem: BUN/Cr 33/2.3, AST 19,025, AlkPhos 12,258, Tbili 3.8

- Admitted to ICU with presumed viral hemorrhagic

Case

- Started on broad spectrum antibiotics and empiric ribavirin
- Cultures of blood, sputum, and urine were all negative for bacterial infection
- Malaria smears x 2 were negative
- Leptospirosis serology were negative

Case

- On hospital day 2:
  - Developed confusion
  - Rapid deterioration to respiratory distress requiring intubation
  - Bleeding started from his GI tract, mouth, and all catheter sites
    - Given 38 units of FFP, 28 units of platelets, 25 units of pRBCs
    - Low dose heparin for DIC
  - ICU team could not stop the bleeding
  - Patient died on hospital day 6

CID 1997; 25:1143-7

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Yellow Fever Review

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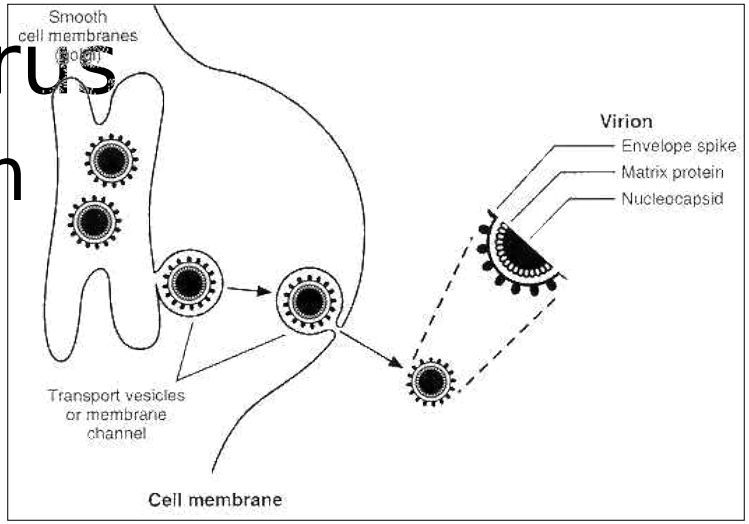
Outline

- Etiology and Flavivirus Review
- Historic Significance
- Epidemiology
- Clinical Presentation
- Vaccine (Prevention)
- Questions

Yellow Fever Virus

- Flaviviridae family, Genus Flavivirus
- (+) ssRNA enveloped virus
  - Replicate in the cytoplasm



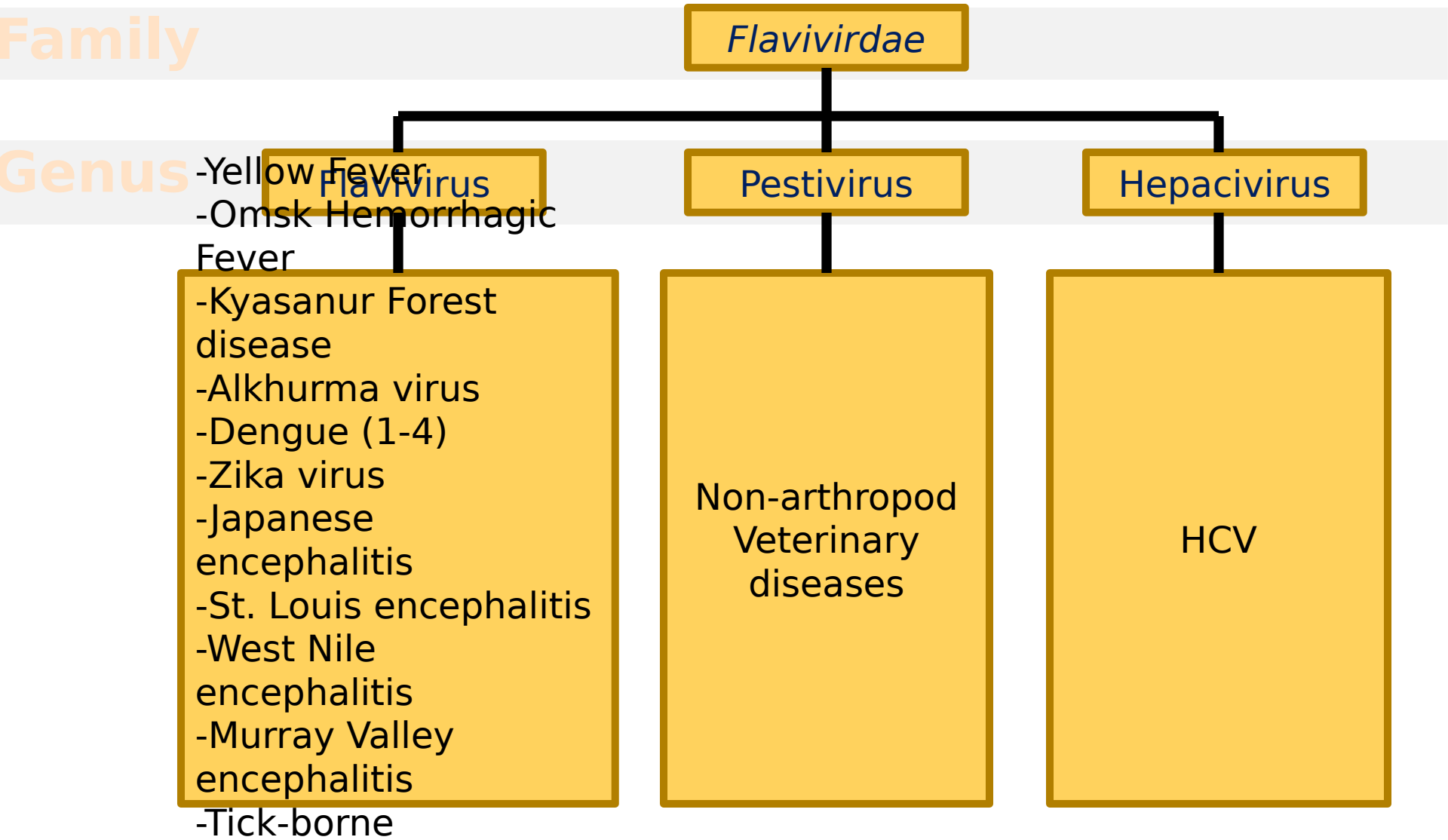
- Flavivirus RNA encode for 10 proteins
  - 3 structural proteins and 7 non-structural proteins

Baron et al, Medical Microbiology, Chapter 54,19

Question

- Yellow Fever is the “prototypical Flavivirus.” Which of the following viruses are **NOT** in the Flaviviridae family?
  - A: Dengue
  - B: Mosquito-borne encephalitis (JE, WNV, St. Louis)
  - C: Hepatitis C
  - D: Tick-borne encephalitis
  - E: Sinbis, WEE, VEE, EEE, Chikungunya

Flaviviridae Family



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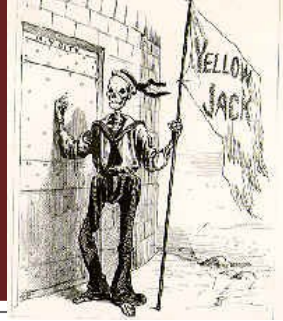
Historic Importance

- First described in the 1600's in the New World
- Imperial Britain's "white man's grave"
  - Fever was romanticized by Coleridge in the Rime of the Ancient Mariner[1]
  - Likely the disease in Wagner's The Flyi Dutchman

- First human disease shown to be due to a "filterable agent" by MAJ Walter Reed

[1] Debbie Lee, **Slavery and the Romantic Imagination, Ch 3.** (available on

Historic Importance



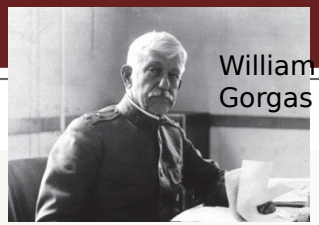
- Disease not previously restricted to “tropics”
  - New York (1668)
  - Philadelphia (1793) 4,000+ deaths
  - Norfolk (1855) 3,000+ deaths
  - New Orleans (1853) 7,849 deaths
  - Mississippi River Valley (1878) 20,000+ deaths

Last major outbreak in the U.S. occurred in New Orleans in 1905

The physical atlas of natural phenomena
by Alexander Keith Johnston, F.R.S.E., F.R.G.S., F.G.S.
William Blackwood and Sons, Edinburgh and London, MDCCCLVI
Also posted on www.iayork.com

Tulane University
Medical School

Yellow Fever Vaccine Timeline



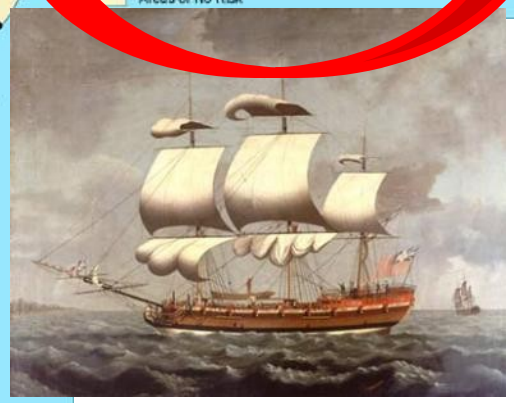
Timeline | **Events in the development and understanding of the YF-17D vaccine**

1648	1762	1793	1802	1878	1881	1898	1899–1901	1927	1937	1945	1951	2006–2009
The first recorded description of an epidemic thought to be yellow fever is made by Mayans in Yucatan.	Thousands of British and American troops die in the British expedition to Cuba. Epidemics in coastal and island communities kill ~10% of the population.	A yellow fever epidemic kills ~10% of the population of Philadelphia, USA.	40,000 French soldiers are killed by yellow fever in Haiti.	20,000 inhabitants are killed in the Mississippi river valley, USA.	Carlos Finlay, a Cuban physician, proposes that yellow fever is carried by the mosquito.	Spanish–American War: 968 American soldiers are killed in combat but over 5,000 die of yellow fever.	Walter Reed shows that yellow fever is spread by mosquitoes.	Stokes and colleagues isolate a strain of yellow fever virus from an infected individual named Asibi, in Ghana. French researchers in Dakar, Senegal, isolate the yellow fever virus from an infected Syrian.	Max Theiler develops the yellow fever vaccine YF-17D.	The WHO grants the use of two substrains of the YF-17D vaccine: 17DD for use in South America and 17D-204 for use in the rest of the world.	The Nobel Prize in Medicine and Physiology is awarded to Max Theiler.	

1903 Panama Canal

TLR, Toll-like receptor; WHO, World Health Organization.

Nat Rev Immunol. 2009 Oct;9(10):741-7. Epub 2009 Sep 1



Mosquito larvae carried in ship's water barrels spread the virus to the Americas

Maps from http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.

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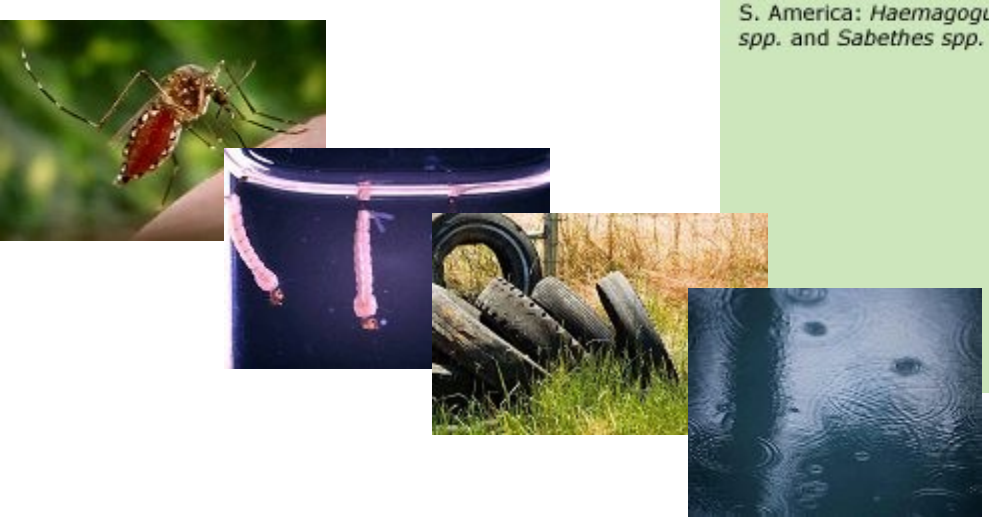
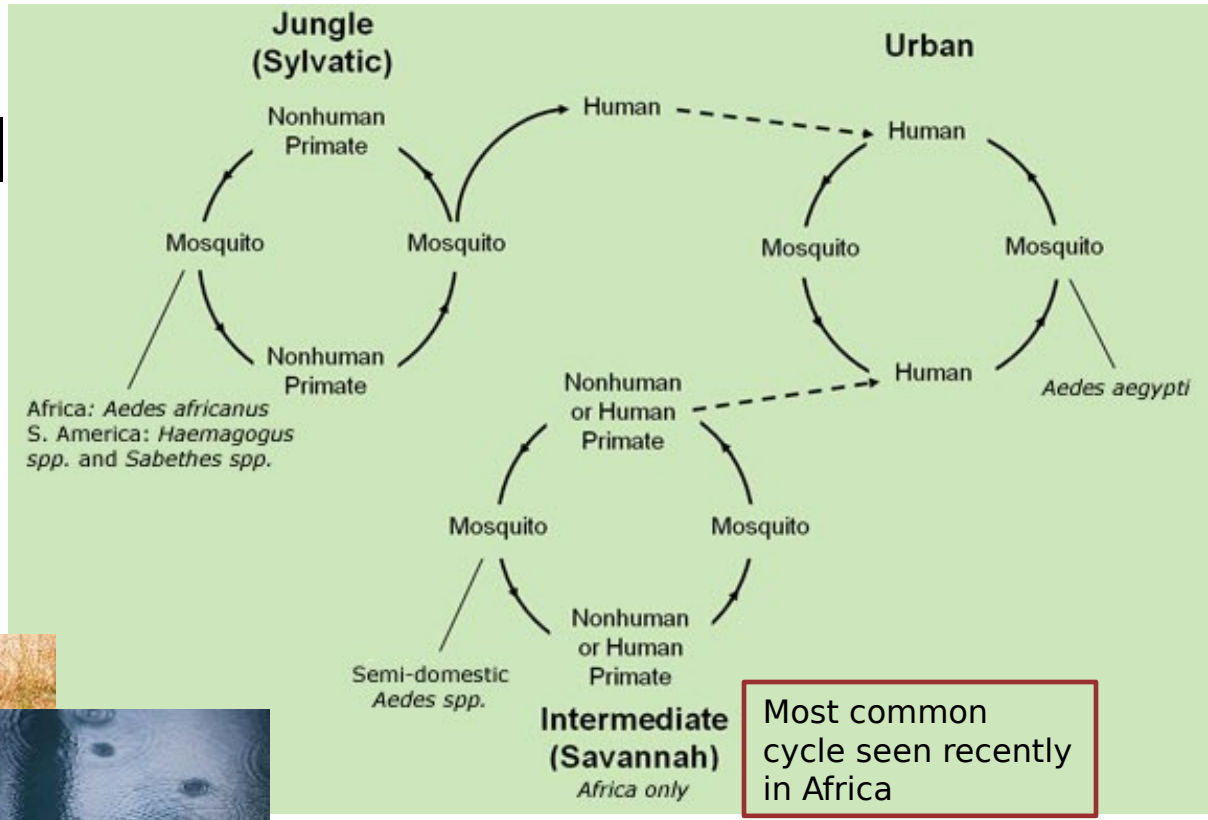
Transmission Cycle

- Sylvatic (jungle) transmission
- Savannah cycl
- Urban Cycle





Sylvatic cycle

- Transmission between nonhuman primates and mosquito species
- African sylvatic cycle:
  - *Ae. africanus* is the principle vector
- American sylvatic cycle:
  - *Haemagogus* sp. is the principle vector
  - Human infections peak during rainy season Dec-May
  - Dead monkeys may herald local sylvatic YF activity
  - Primary method of human transmission in Americas
- Demographic: mostly males age 15-45yo

Barrett A., Higgs S.: Yellow fever: a disease that has yet to be conquered. *Annu Rev Entomol* 52. 209-2

Savannah Cycle

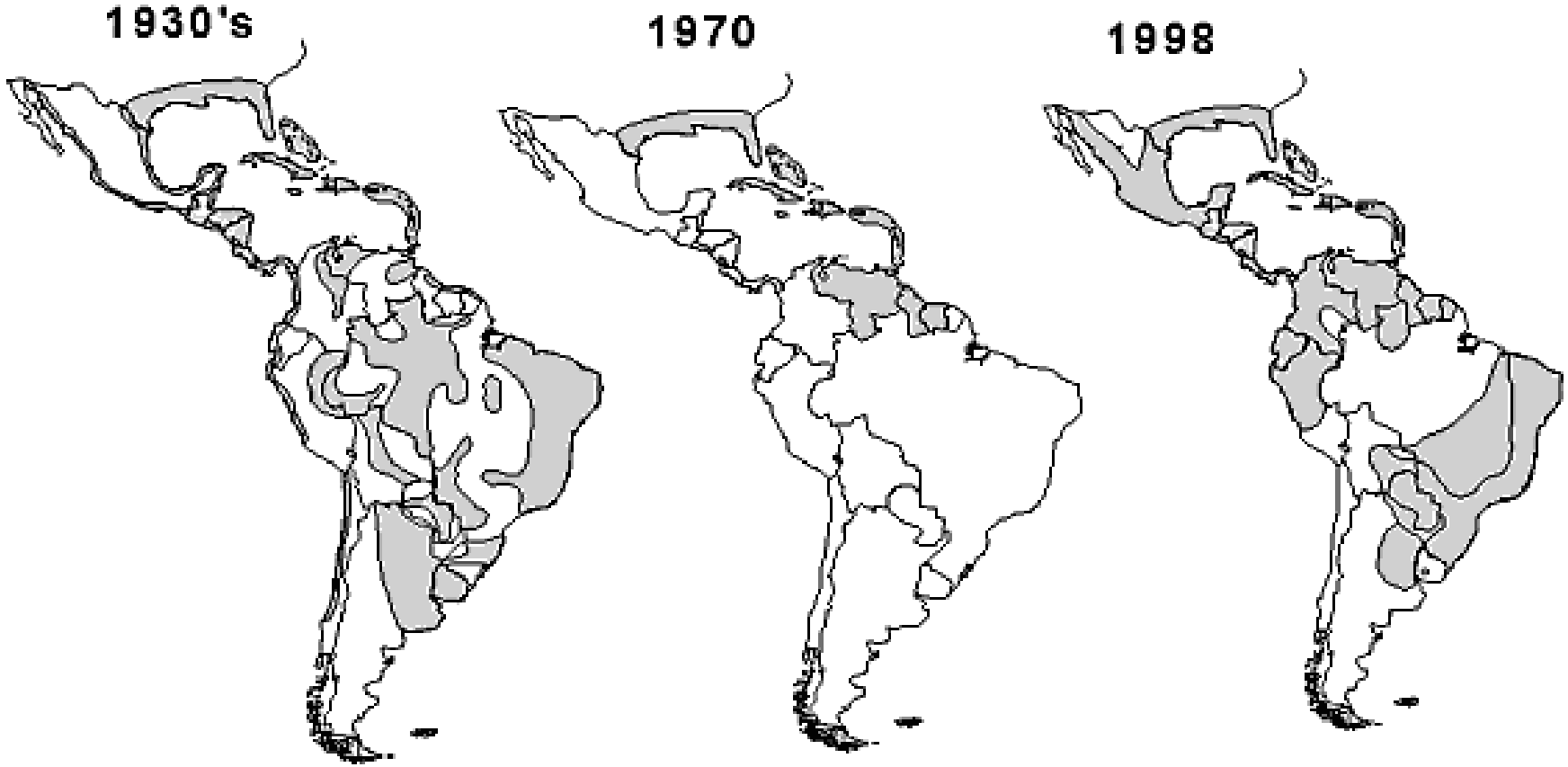
- An intermediate cycle between Sylvatic and Urban described in Africa
- Characteristic:
  - non-Ae. aegypti vector
  - Epidemics occur
- Demographic: both sexes and all ages

Urban Cycle

- Associated with epidemics and substantial morbidity and mortality
- *Ae. aegypti* is the principle vector
- Elimination of *Ae. aegypti* in the Americas led to elimination of Urban YF
- Demographic: both sexes and all ages

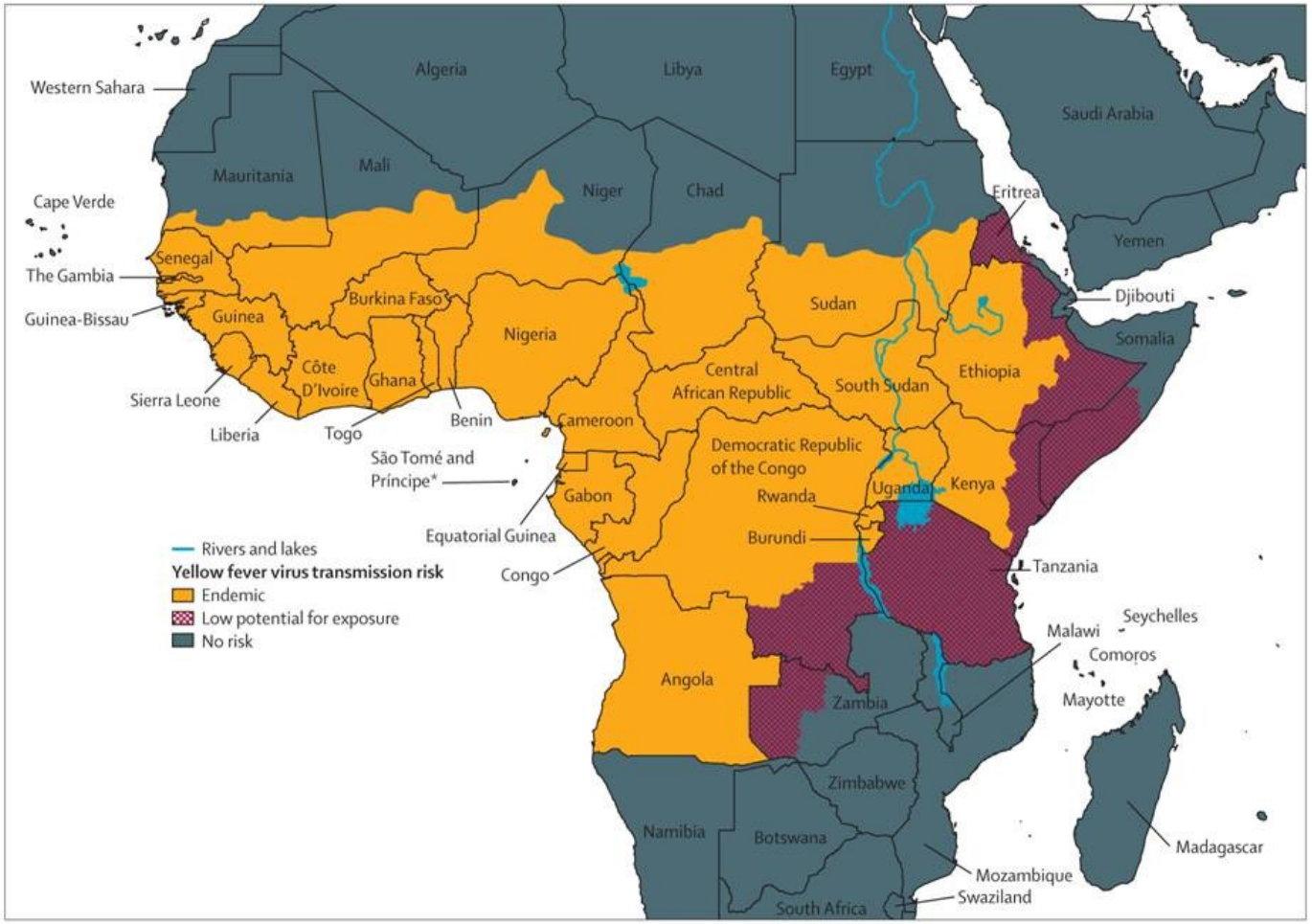
Staples J.E., Monath T.P.: Yellow fever: 100 years of discovery. *JAMA* 300. (8): 960-962.2

Resurgence of Ae. aegypti



Gubler DJ . Resurgent Vector-Borne Diseases as a Global Health Problem. EID 1998 Jul-Sep;4(3):4

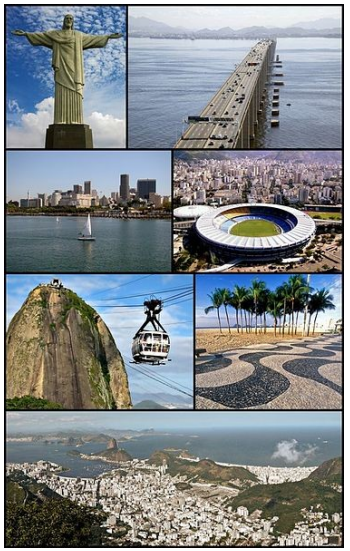
Current African Distribution



Jentes ES. Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 2011;11:622-32.

Current Americas Distribution

Risk is not holoendemic !



Jentes ES. Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 2011;11:622-32.

Comparing YF: Africa vs. Americas

AFRICA

- **5000*** cases a year
- Vector: *Aedes spp.*
- Urban, Savannah, Sylvatic
- Prone to Epidemics

*likely underestimated

AMERICAS

- **50** cases a year
- Vector: *Haemagogus and Aedes*
- Sylvatic Cycle only
- “Events”

Recent African Epidemics

COUNTRY	DATE	CASES	DEATHS	CASE FATALITY RATE	VACCINES GIVEN
Nigeria	1990	102 (hospitalized)	81	79%	
Sudan	2003	178 (suspected)	27	15%	185,000
Uganda	DEC 10	226 (suspected)	53	23%	905,000
Ivory Coast	JAN 11	64 (suspected)	25	39%	840,000

Vaccination Source: WHO Website
http://www.who.int/csr/don/archive/disease/yellow

Nigeria: West Afr J Med. 2010 Mar-Apr;29(2):91-7.
Sudan 2003: EID. 2004 Sep;10(9):1668-70.
Congo 2009: Wkly Epidemiol Rec. 2009 May 8;84(19):161.
IC & Uganda 2011: Wkly Epidemiol Rec. 2011 Jan 28;86(5):37-8

More Recent Epidemics

COUNTRY	DATE	CASES	DEATHS	CASE FATALITY RATE	VACCINES GIVEN
Democratic Republic of Congo	JUN 13	51 (suspected)	19	37%	503,426
Ethiopia	MAY 13	6	??	??	527,000
Chad	DEC 12	139 (suspected)	9	6%	1 million +
Sudan	NOV 12	732 (suspected)	165	23%	3.4 million +
Cameroon	DEC 11	23	7	30%	1.2

Recent American "Events"

- Brazil 2002: 36 cases, 12 deaths (33% CFR)
- Venezuela 2004: 2 confirmed, 1 death (50% CFR)
- Brazil 2007: 48 confirmed, 13 deaths (32% CFR)
- Paraguay 2008: 22 confirmed, 6 deaths (27% CFR)

Table 2 **Number of cases, number of deaths and case-fatality rate (CFR) for yellow fever in South America, 2007**
Tableau 2 **Nombre de cas, nombre de décès et taux de létalité (TL) pour la fièvre jaune en Amérique du Sud, 2007**

Country – Pays	No. of cases – Nombre de cas	No. of deaths – Nombre de décès	CFR (%) – TL (%)
Bolivia – Bolivie	6	6	100
Brazil – Brésil	13	10	77
Colombia – Colombie	6	6	100
Peru – Pérou	23	18	78

Wkly Epidemiol Rec. 2009 Mar 27;84(13):97-104.
Brazil02: Rev Soc Bras Med Trop. 2009 Sep-Oct;42(5):523-31

Recent Imported "Events"

World Health Organization

Health topics | Data and statistics | Media centre | Publications | Countries | Programmes and projects

Search

Global Alert and Response (GAR)

- GAR Home
- Alert & Response Operations
- Diseases
- Global Outbreak Alert & Response Network
- Biorisk Reduction

2001 - Imported case of yellow fever in Belgium

12 November 2001

Disease Outbreak Reported

The Belgian Ministry of Health has confirmed a case of yellow fever imported into Belgium. The patient had returned from a holiday in The Gambia where she initially became ill. She returned to Belgium on 8 November. Tests on clinical samples performed at the the Bernhard Nocht Institute, Hamburg, Germany, have confirmed the diagnosis.

She is currently stable and receiving treatment in a Belgian hospital. It has been

Recent U.S. Imported“Events”

YEAR	COUNTRY	PATIENT	OUTCOME	VACCINATED
1996	BRAZIL	45 yo male (Amazon river)	DEATH	NO
1999	VENEZUELA	48 yo male (Rainforests)	DEATH	NO
2002	BRAZIL	47 yo male (Amazon river)	DEATH	NO

CID 1997; 25:1143-7
MMWR 2000;49:303
MMWR 2002; 51:

East African YF epidemiology

- Differences in regional epidemiology
  - 7 genotypes of YF distributed across Africa
- Eastern and Central Africa have few YF epidemics
  - Usually associated with periods of civil unrest
  - Also with large population movements into areas with endemic YF
- Large Urban YF epidemics are less common in East Africa

Ellis B.R., Barrett A.D.: The enigma of yellow fever in East Africa. *Rev Med Virol* 18. (5): 331-3

West African YF epidemiology

- West Africa genotypes I and II are prevalent
- Epidemic YF is historically more common
- May occur during stable socio-political times and without mass movements of people

Ellis B.R., Barrett A.D.: The enigma of yellow fever in East Africa. *Rev Med Virol* 18. (5): 331-3

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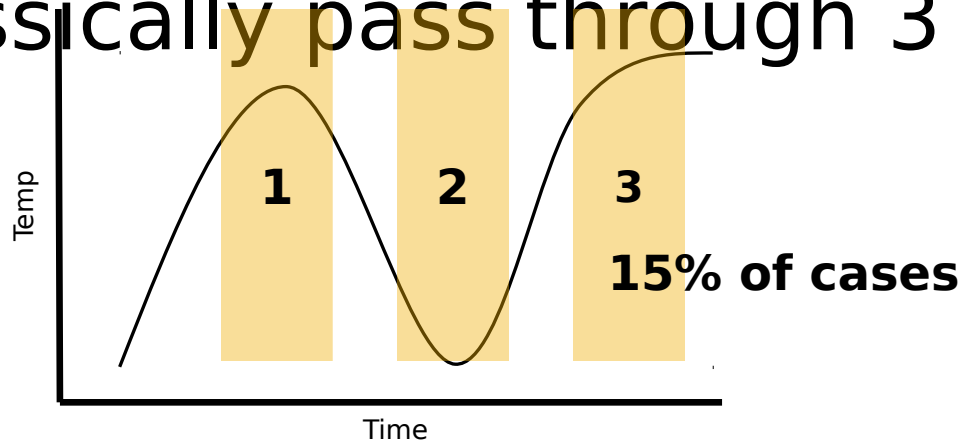
Spectrum of Clinical Illness

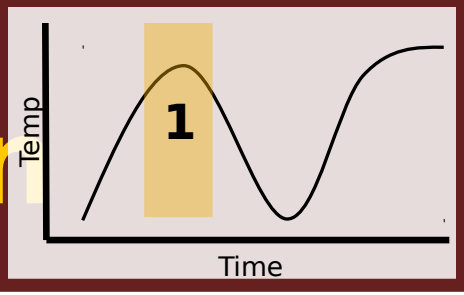
- Subclinical infection
- Abortive, nonspecific febrile illness w/o jaundice
- Life-threatening disease with fever, jaundice, renal failure and hemorrhage

Clinical Presentation

- Incubation period of 3 to 6 days
- Majority of infections are inapparent or mild
- Severe cases classically pass through 3 phases:
  - Infection
  - Remission
  - Intoxication



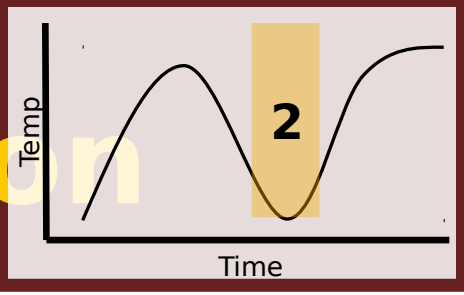
3 Phases: Infection



- Mild YF will only pass through this phase
- Acute febrile illness of short duration often <48H
- Characterized by:
  - Fever, headache, mylagias, other mild constitutional sx
  - Proteinuria my be present
  - Leukopenia (1.5 – 2K) with relative neutropenia
  - Faget's Sign: bradycardia in relation to fever
    - Classically described in YF, but found in other infections

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London,

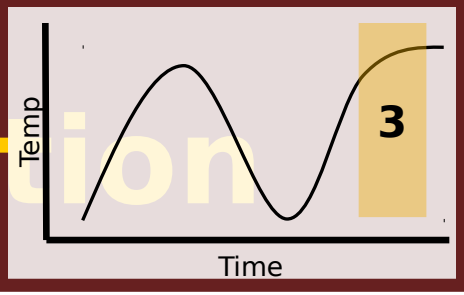
3 Phases: Remission



- Seen in severe cases
- Diminishment of fever
  - With improvement in clinical status
- Lasting up to 24-48 hours
- In very severe YF cases, remission period may be short or absent

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London,

3 Phases: Intoxication



- Severe and widespread necrosis in liver
  - Jaundice – clinical sign c/w case-fatality rate 20-50%
- Myocardial and Renal dysfunction
- Ultimately leading to Hemorrhagic Fever:
  - Hepatic failure, encephalopathy, hemorrhage
  - Hematemesis is characteristic
  - Laboratory Findings:
    - Leukopenia (low WBC) and thrombocytopenia (low platelets)
    - Elevated liver enzymes and abnormalities on clotting tests
      - **AST** >> ALT

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London,

Vomito negro

http://itg.content-e.eu/Generated/pubx/161/arboviruses/yellow_fever.htm

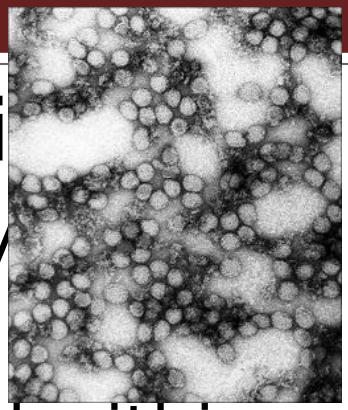
Diagnosis

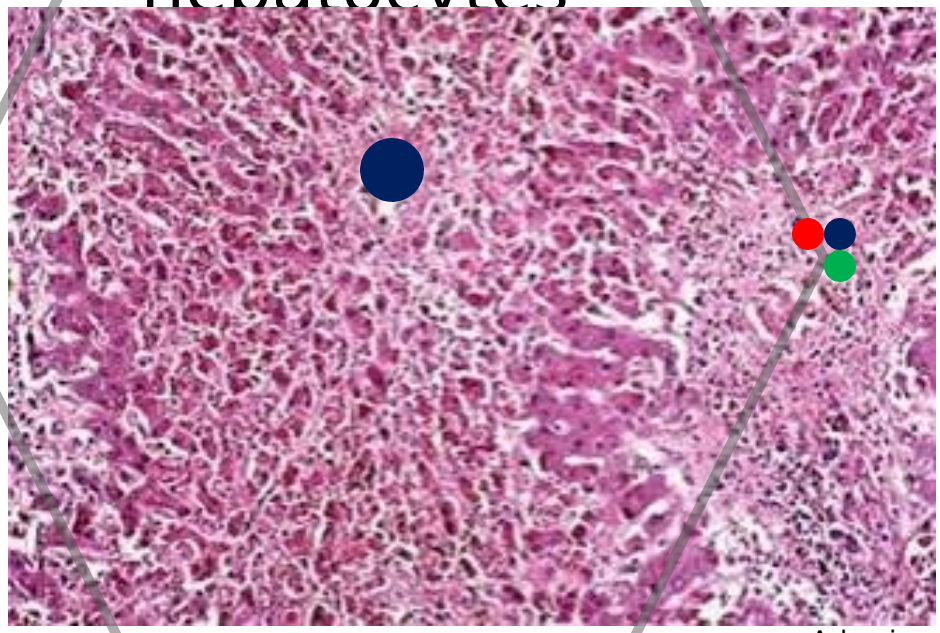
- Clinical Diagnosis
  - h/o travel to endemic area within the incubation period

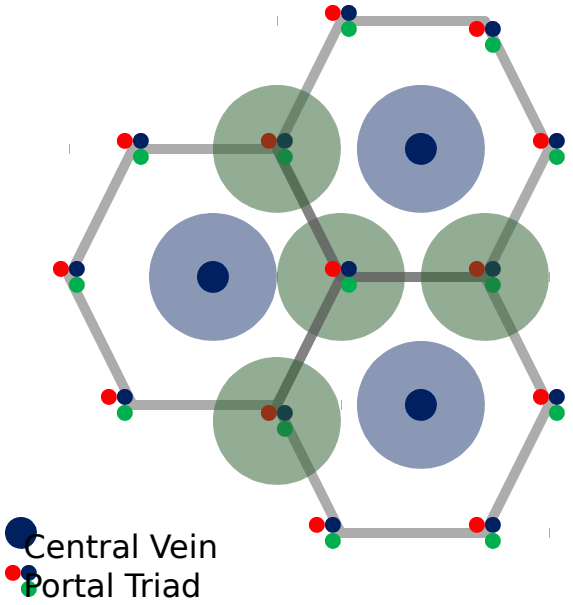
- Advanced Diagnostics:
  - Virus Isolation (culture)
  - Rapid Diagnostics
    - PCR
    - Antibody or Antigen detection (ELISA)
      - IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
      - Use with caution as Ab/Ag may not be detected late in disease
      - Cross reaction with other flaviviruses (also previous YF vaccination)
    - Neutralization Ab are more specific for YF

Liver Histology: Autopsy or Biopsy

- mid-zonal coagulative necrosi
  - with sparing of periportal hepatocy
  - minimal inflammation is seen
  - viral antigen may be demonstrated within hepatocytes







Picture from alarabiya.net

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London,

Treatment Overview

- Supportive Care -- no specific therapy
  - Maintain nutrition and prevent hypoglycemia
  - NG tube to prevent gastric distention
  - Treatment of hypotension (IVF, pressors)
  - Supplemental oxygen
  - Correction of bleeding abnormalities
  - Dialysis
  - Treatment of secondary infections
  - Treatment of DIC

Certain medications should be avoided, such as aspirin or other non-steroidal anti-inflammatory drugs (such as ibuprofen and naproxen), because these may increase the risk for bleeding.

PROTECT FROM FURTHER MOSQUITO EXPOSURE

Alternative Treatments

- Stress-dose steroids not clearly indicated
- Ribavirin is active against YF in vitro
  - Monkeys model showed no benefit
  - Hamster model with improved formulation did show benefit
  - Likely requires extremely high drug levels to achieve effect in humans

J Nat Prod 1992 Nov;55(11):1569-81.
Am J Trop Med Hyg 2004 Sep;71(3):306-1

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Yellow Fever Control

- Vector control is critical to control of YF
  - Elimination of *Ae. aegypti* results in complete control of urban cycles
  - Also controls Dengue transmission & other diseases
- Vaccine critical to control in endemic zones
  - Sylvatic YF cannot be eliminated
- Vaccine also critical in keeping YF out of areas susceptible to re-emergence
  - Areas with vector (*Ae. aegytpi*) and host (human)

Yellow Fever Vaccine

- 2 live-attenuated YF vaccines were developed
- Both developed from serial passage of human-derived YF
  - FNV: passage in mouse brain
  - 17D: passage in chicken embryo tissue

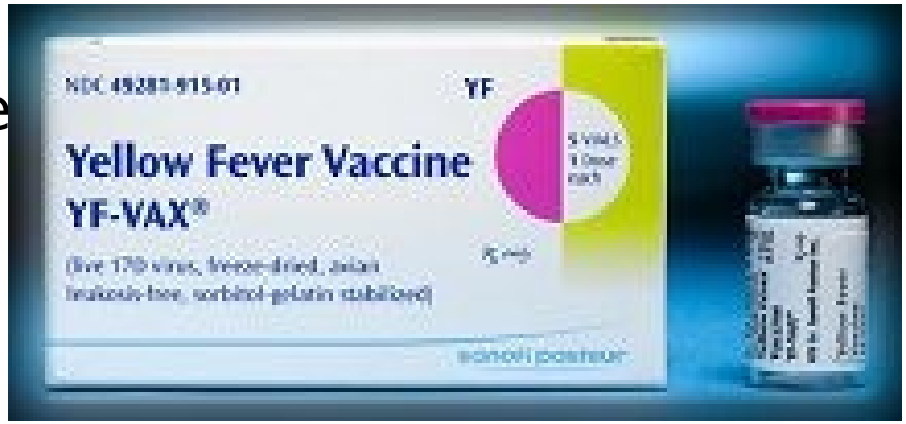
Yellow Fever Vaccine: FNV

- Between 1939-52 administered to nearly 40 million people in West Africa
  - Effectively reduced YF incidence in the region
- Associated with large numbers of encephalitis cases in children
  - Vaccine not recommended for children less than 10yo
  - Manufacture discontinued in 1980

WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fe

Yellow Fever Vaccine: 17D

- Has remained in continuous use since 1936
  - Over 400 million doses give
  - Protects:
    - 90%/10days
    - 99%/30days



- Long-lasting immunity
  - Countries may require boosting every 10 years
  - Studies have shown neutralizing Ab decades after dose
    - 81% of US WWII veterans with Ab after more than 30yrs

1. WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.
2. Poland JD, Calisher CH, Monath TP. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59:895

Yellow Fever Vaccine: Use in Endemic Countries

- WHO recommends incorporation into routine infant and child immunizations
  - Given between 9 and 12 months of age
  - Severe YF more common in infants and young children in outbreaks of YF in endemic zones

- 32 of 44 countries endemic for YF have partial or national expanded programs for YF immunization
  - Despite this, coverage less than 50% in these countries

WHO. Yellow fever vaccine. www.who.int/vaccines/en/yellowfe

YFV: Emergency Vaccination Campaigns

- Surveillance is important in the detection of YF outbreaks
- Largest mass vaccination campaign:
  - Southern Mali in April 2008
  - 6000 HCP and 2000 volunteers vaccinated 6 million
- In mass vaccination vaccine can be given to children as young as 6 months (instead of 9mo)
  - Manufacturer contraindicates use in infants <9mo

WHO. Mali: 6 million vaccinated against yellow fever. 2008 at: www.who.int/features/2008/mali_vacc
Health information for international travel, 2008. Atlanta: CDC, 2007.

Yellow Fever Vaccine: Contraindications

- Three major contraindications:
  - Immunosuppression (YF Vaccine is a Live Virus)
  - Age younger than 6 months
  - Allergy to eggs
  - History of thymus disorder
    - Including myasthenia gravis, thymoma, or prior thymectomy
- Caveats:
  - HIV not a strict contraindication (unless pt has AIDS)
  - Should be avoided in pregnancy / breast feeding
  - Should be avoided acute or febrile illness

WHO. Vaccine-preventable diseases and vaccines. In: International travel and health,

YF Vaccine: Reactions

- Common
  - Injection site inflammation (1-5 days)
  - Fever, headache, body aches (5-10 days)

- Severe
  - Hypersensitivity reactions (including anaphylaxis)
  - Yellow fever vaccine-associated neurologic disease (YEL-AND)
  - Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)

YFV:
YF-associated Viscerotropic disease

- First recognized in 2001
- Incidence: 0.3 to 0.4 per 100,000 vaccinated persons
  - Some vaccine lots may have higher rates
- Presents 2-5 days after YF vaccine
  - Febrile illness with multi-organ failure
  - Indistinguishable from natural YF disease
- 60% case fatality rate

If you suspect a vaccine related adverse event: Vaccine Adverse Events Reporting System (VAERS)

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:607

YFV:
YF-associated Viscerotropic disease

- Higher Risk population:
  - Individuals older than 60 yo
  - Individuals with thymus disorders
  - Primary vaccination in non-immune individuals

- Risk seems to be much lower in infants/children
  - Incidence of 1 case per 10million doses in routine child immunizations

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:607

YFV:
YF-associated Neurotropic disease

- Rare: incidence 0.4 per 100,000 vaccinations

- Mulitple presentations:
  - Post-vaccine encephalitis
  - Autoimmune involvement of central and peripheral nervous system
    - Including Guillain-Barre syndrome

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:607

Yellow Fever Vaccine: Encephalitis in Infants

- Young infants at increased risk
- Has led to the lack of recommendation consensus for infants 6-8 months who need vaccine

Yellow Fever Vaccine: Risks for Travellers

- Risk of illness / death for a 2-week stay
  - West Africa is 50 per 100,000 / 10 per 100,000
  - South America is 5 per 100,000 / 1 per 100,000

- These are rough estimates based on the risk to indigenous populations, during peak transmission

CDC website: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever

Yellow Fever Vaccine: Recommendations for Travelers

- HCP giving advice must remain current in YF endemic regions
  - Review current maps (WHO, CDC, TRAVAX)
  - Carefully scrutinize itinerary to best determine risk
- Balance risk of YF exposure and YF immunization
- If vaccination is only to satisfy an international requirement (as opposed to decreasing risk of infection), efforts should be made to obtain a waiver letter

Careful Scrutiny of Itinerary

- Example of travel to Argentina
- YF risk is isolated in the North
- Only parts of provinces affected

Map from Travax Encompass

Yellow Fever Vaccine Waiver

Figure 2-2. Example International Certificate of Vaccination or Prophylaxis (ICVP) medical contraindication to vaccination

MEDICAL CONTRAINDICATION TO VACCINATION
Ceontre-indication médicale à la vaccination

This is to certify that immunization against
Je soussigné(e) certifie que la vaccination contre

_____ for
(Name of disease – Nom de la maladie) pour

_____ is medically
(Name of traveler – Nom du voyageur) est médicalement

contraindicated because of the following conditions:
contre-indiquée pour les raisons suivantes:

_____

_____

_____

_____
(Signature and address of physician)
(Signature et adresse du médecin)

Image available on CDC website: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fe

Outline

- Etiology and Flavivirus Review
- Historic Significance
- Epidemiology
- Clinical Presentation
- Vaccine (Prevention)
- Questions

For More Information…

- **Country**
- http://wwwn.cdc.gov/travel/yellowBookCh5-MalariaYellowFeverTable.aspx

- **Current Risk Maps**
- http://wwwn.cdc.gov/travel/yellowBookCh4-YellowFever.aspx

- **Outbreaks Occurring Around the World**
- Travel Notices www.cdc.gov/travel
- Information by country is also available in the Yellow Fever section of the CDC's travel health book, *Health Information for International Travel,* also known as the Yellow Book.